ABSTRACTS

Invited Speakers

IS01

Gene therapy - new horizons in ophthalmology

Associate Professor Mirjana Bjeloš, M.D., PhD

DOI: https://doi.org/10.26800/LV-144-supl2-IS01

Reference Centre of the Ministry of Health of the Republic of Croatia for Pediatric Ophthalmology and Strabismus, University Eye Department, Luxturna Treatment Centre, University Hospital Sveti Duh School of Medicine, University of Osijek

Over a decade of research and development culminated in December 2017 with United States Food and Drug Administration (FDA) approval of voretigene neparvovec-rzyl (VN) treatment for RPE65 mutation-associated inherited retinal dystrophy (IRD). This is the first approved gene therapy for a hereditary genetic disease and the first and only pharmacologic treatment for an IRD. By the end of 2018 VN has been authorized for use in the EU. Thus, the aim of gene therapy using voretigene neparvovec is to improve visual function and prevent blindness by halting the progressive natural course of disease. The term itself, inherited retinal dystrophy, encompasses a wide range of blinding retinopathies, with marked phenotypic and genotypic diversity, characterized by anatomical and functional damage of retinal cells. Worldwide, 1:2000 individuals worldwide suffer from IRDs. RPE 65 dystrophy, affecting 1:200000, causes Leber congenital amaurosis type 2 (LCA2) and pigmentary retinopathy type 20 (RP20). RPE65 is expressed in RPE cells, encoding a protein RPE65, retinoid isomerohydrolase, crucial in the visual cycle. Both RP and LCA are devastating diseases not just because these children have terrible vision at birth, but because their vision is getting progressively worse ending in complete blindness. Age of onset of biallelic RPE65 mutation–associated retinal dystrophy is variable and can range from infancy into young adulthood. Symptoms include nystagmus, tendency to fixate on light, nyctalopia, constricted visual fields and flat scotopic signals on electroretinogram (ERG). During childhood, in most cases, the retina appears pale but without characteristic pigment accumulation.

Because of the complexity and variability of signs and symptoms, genetic testing is a must to enable classification of disease.

VN utilizes AAV2 as a vector to deliver a single-strand DNA molecule with the coding sequence (cDNA) of the RPE65 transgene to the RPE. This therapeutic strategy, called gene augmentation, ameliorates the lost function through delivery and expression of a normal gene. For this delivery, vitrectomy and iatrogenic retinal detachment should be induced. Normal RPE65 protein now can be manufactured, restoring the visual cycle.

Treatment is administered to each eye on separate days, no fewer than 6 days and no more than 18 days apart. Patients undergo treatment only once because this treatment has a long lasting effect.

To be treated with VN two major criteria must be fulfilled. First, the patient must have biallelic RPE65 mutation and there must be a sufficient number of viable cells. VN safety profile is consistent with vitrectomy and subretinal injection procedure.

Measurable improvement from as early as day 30 is achieved in 93% of patients who all benefited from improved functional vision and majority (72%) achieved maximum improvement.

In case of biallelic RPE65 mutation refer the patient to Luxturna treatment centers. The University Eye Department University Hospital Sveti Duh in Zagreb, Croatia was designated as the 6th world' s gene therapy center in July 2020., after successful full reimbursement of the drug by the Croatian National Health Insurance Fund in January 2020.

The multidisciplinary team consists of a pediatric ophthalmologist, an IRD specialist, three retinal surgeons with experience in subretinal application, pharmacist and a geneticist. In the 1.5 year of the designation the Centre has successfully treated 8 Croatian patients and 7 non-Croatian EU citizens.